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Validation of multi-scale models for fibrosis. Comment on "Towards a unified approach in the modelling of fibrosis: A review with research perspectives" by M. Ben Amar and C. Bianca

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Over the last few decades, medical research has started to emphasise the need for an integrative approach that could unravel the progression of various diseases across different spatial and temporal scales, and the links between the different phases of disease progression [2, 6]. Among these diseases, the fibroproliferative disorders are a leading cause of morbidity and mortality by affecting tissues and organ systems [11], and thus investigating and understanding the common mechanisms behind fibrogenesis might lead to the development of new therapies [9, 6].

In [1], the authors presented a brief review of the current state of the art in mathematical modelling of various fibroproliferative disorders, with an emphasis on the unified approach that needs to be taken when investigating these disorders. While the need for an integrative, multi-scale and multi-organ approach has been recognised by experimental scientists [8], the amount and variety of information generated by basic research is still difficult to understand. To accelerate the development of clinical treatments for fibrosis it is necessary not only to validate experimental models [10], but also to derive and validate multi-scale mathematical models. As emphasised also in [1], various single-scale fibrogenesis models (mainly described by ODEs and PDEs) have been validated against patient data (usually microscale or mesoscale data). Nevertheless, there are many other mathematical models

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that focus only on analytical approaches (equally important in the modelling process to determine the appropriateness of model equations).

A particularly complex issue is the validation of multi-scale models, which are being developed more and more often to investigate, for example, wound healing [3, 7] or cancer dynamics [4]. Due to a lack of data – from same *in vitro* or *in vivo* experiments – that links information regarding fibrogenesis across scales, it is very difficult to validate these multi-scale mathematical models. Moreover, because of data stochasticity, parameter sensitivity needs to be performed to study the reliability of the model. The multi-scale aspects of these models require the use of different sensitivity methods for different mathematical equations (e.g., discrete or continuous) valid at different scales. Hence, despite the great potential of these multi-scale models to provide a unified description of the fibrosis process, their complexity combined with a lack of serious model validation makes them currently unaccessible to experimental biologists and clinicians (who usually do not read journals that present only abstract results).

Closer collaborations between mathematicians and experimentalists are necessary to generate a comprehensive collection of uniform data (i.e., data from patients with the same immune response against the same fibroproliferative disorder, and not from separate experimental studies performed under different conditions), which could be then used for model calibration and parameter estimation. It should be emphasised that current approaches focus mainly on collecting data existent the literature and generated through different experimental conditions (see, for example, [5]). Such data is unlikely to be of significant use for quantitative predictions, although it could still generate qualitative predictions regarding the variety of responses that might be observed in the biological system. Even if *in vitro* experiments are specifically designed to validate specific multi-scale models, there is always the possibility of observing discrepancies between the experiments and the numerical results (as noticed in [7]), which challenges model assumptions and requires the development of new experimental and modelling approaches to address these discrepancies.

To conclude, testing the reliability of these multi-scale models is the first step towards their use to propose quantitative and qualitative hypotheses that could improve fibrosis treatments.

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